PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference 17166 KB	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/HU2004/000069	International filing date *(day/month/year)* 30.06.2004	Priority date *(day/month/year)* 02.07.2003

International Patent Classification (IPC) or national classification and IPC
C07D495/04, A61K31/4365, A61P7/02

Applicant
EGIS GY GYSZERGY R RT.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☒	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.02.2005	11.10.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/HU2004/000069

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-12 as originally filed

   Claims, Numbers

   1-10 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/HU2004/000069

Box No. II Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   - ☒ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

V. CITATIONS AND EXPLANATIONS

The following documents are mentioned in this report.

WO-A-03 51362 (A)
WO-A-04 81016 (B)

The novel feature of the process of claim 1 is the use of an aprotic solvent in the process of preparing amorphous clopidogrel hydrogen sulphate, followed by addition to a second solvent and isolation of the product by filtration. Claims 2-10 which describe preferred embodiments of the process of claim 1 are novel by consequence. Claims 1 to 10 therefore meet the Novelty requirements of Article 33(2) PCT.

Document (A) describes a number of processes for the preparation of clopidogrel hydrogensulphate, either as one of the crystalline forms I-V, or as the amorphous form. In examples 13 to 15, the amorphous form is prepared by dissolving clopidogrel hydrogensulphate in methanol, then by adding the solution so obtained to a second less polar solvent, being toluene or diethyl ether. On page 6, lines 13 to 29, a general process for preparing amorphous clopidogrel hydrogensulphate is given in which the hydrogensulphate is prepared in methanol or ethanol, and in which the solution is then added to an anti-solvent in order to precipitate the desired amorphous form. In another process, an acetone solution of clopidogrel hydrogensulfate is evaporated to dryness in order to obtain the amorphous form (example 17). The presently claimed process, in which an aprotic solvent is used to dissolve the clopidogrel free base, and in which a solution of the hydrogensulfate is added to a second aprotic solvent, appears to lead consistently to the formation of the amorphous form of clopidogrel which may be isolated by filtration. Thus the presently claimed process appears to be advantageous because the processes described in document (A) often lead to the formation of other polymorphic forms. Inventive step (Article 33(3) PCT) can be recognised because the problem of providing a process for the preparation of stable amorphous clopidogrel hydrogen sulphate is solved in a non obvious manner (see examples).

VI. CERTAIN DOCUMENTS CITED

At present no priority document is available. The examination has been carried out assuming that the priority date is validly claimed. If during the subsequent procedure (e.g. EPO examination) the priority date is found to be invalid for some or all of the presently claimed subject matter, the intermediate document (B) may be taken into consideration for the evaluation of Novelty and/or inventive step.

VIII. CERTAIN OBSERVATIONS ON THE INTERNATIONAL APPLICATION

Claim 1 does not meet the requirements of Article 6 PCT due to lack of clarity. The skilled man cannot determine what is meant by "A-type solvent" or "B-type solvent" without reference to the description (cf. Rule 6.2(a) PCT). Also, the term "less polar aprotic solvent" used in claim 3 appears to have no generally accepted meaning.